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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,853	11/07/2000	Fulvio Mavilio	1303-110	5693

23117 7590 01/14/2004

NIXON & VANDERHYE, PC
1100 N GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,853	MAVILIO, FULVIO	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11 and 13-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 13-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and response received on 10/7/03 has been entered. As requested, claim 12 has been canceled, and new claims 19-22 have been entered. Claims 11 and 13-22 are pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of claims 11-16 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 102

The rejection of claims 17-18 under 35 U.S.C. 102(b) as being anticipated by Murry et al. (1996) J. Clin. Invest., Vol. 98 (10), 2209-2217 is withdrawn in view of applicant's amendments to the claims.

Applicant's amendments to the claims and addition of new claims has resulted in the following new grounds of rejection under 35 U.S.C. 102(a).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 11 and 13-22 are newly rejected under 35 U.S.C. 102(a) as being anticipated by Lattanzi et al. (May, 1998) J. Clin .Invest., Vol. 101 (10), 2119-2128. The applicant's claims new or amended recite genetically-modified fibroblasts transduced with a therapeutic gene and transiently expressing a muscle lineage commitment gene. The applicant further claims said fibroblasts which are dermal fibroblasts, and wherein the muscle lineage commitment gene is MyoD. In addition, the applicant claims methods for the myogenic conversion of genetically modified dermal fibroblasts comprising transducing dermal fibroblasts with a therapeutic gene and an adenoviral vector encoding a muscle lineage commitment gene such as MyoD wherein the genetically modified dermal fibroblasts are myogenically converted at a rate of greater than 40%.

Lattanzi et al. teaches *ex vivo* methods of myoconversion of fibroblasts comprising the transduction of dermal and muscle fibroblasts with an adenovirus encoding MyoD resulting in the myoconversion of these cells at rates greater than 40% (Lattanzi et al., page 2122, Table I). Lattanzi et al. further teaches methods of myoconversion of dermal fibroblasts which have been further transduced with a therapeutic gene such as dystrophin (Lattanzi et al., page 2127, column

1, paragraph 1, and column 2, paragraph 1). Thus, by teaching all the elements of the claims as written, Lattanzi et al. anticipates the invention as claimed.

Claim Rejections - 35 USC § 103

The rejection of pending claims 11 and 13-16 under 35 U.S.C. 103(a) as being unpatentable over WO 96/09373, 28 March 1996, hereafter referred to as Watt et al., in view of Choi et al. (1990), PNAS, Vol. 87, 7988-7992, and further in view of Murry et al. (1996) J. Clin. Invest., Vol. 98 (10), 2209-2217 is withdrawn over amended claims 11 and 13-16 and newly applied to amended and new claims 17-22. Please note however that claims 11 and 13-16 are newly rejected under 35 U.S.C. 103(a) below. Applicant's arguments have been fully considered as they apply to the amended and new claims but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant claims as amended recite genetically-modified fibroblasts transduced with a therapeutic gene and transiently expressing a muscle lineage commitment gene. The applicant further claims said fibroblasts which are dermal fibroblasts, and wherein the muscle lineage commitment gene is MyoD.

The applicant argues that none of Watt et al., Choi et al., or Murry et al., separately or in combination teach rates of myoconversion of dermal fibroblasts of 40% or greater and the one of skill in the art would not have predicted such a high rate of conversion in dermal fibroblasts transduced with the adenovirus encoding myoD taught by Murry et al. because Murry et al. used cardiac fibroblasts not dermal fibroblasts and only observed a myoconversion rate of 14%. The

applicant also argues that such low rates of myoconversion as taught by Watt et al., Choi et al., and Murry et al. have no practical use as a therapeutic intervention. In response, claims 17-22 are product claims, not method claims. The rate of myoconversion of these cells is not a limitation in the claims as written and furthermore, patentability of product claims is based on their structure and not on their intended use in therapy. The MPEP states that,".. in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto* , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). Thus, applicant's arguments regarding rates of myoconversion taught by Watt et al., Choi et al., and Murry et al. are not compelling in overcoming the combined teachings of Watt et al., Choi et al., and Murry et al. for making a dermal fibroblast transduced with a vector encoding dystrophin and further transduced with an adenovirus encoding MyoD. Likewise, applicant's arguments that the high rate of myoconversion demonstrated by the applicant's represents an unexpected result which renders the claims non-obvious is not persuasive as the instant claims are not directed to methods of myoconversion but to the transduced cells themselves.

The previous office explained that Watt et al. teaches the transduction of dermal fibroblasts which have been removed from a patient with a muscular disorder with a vector encoding dystrophin, a gene therapeutic for muscular dystrophy (Watts et al., page 6, and pages 23-24, claims 1-24). Choi et al. supplements Watt et al. by teaching that primary dermal fibroblasts transduced with a retrovirus encoding myoD differentiate into striated mononucleated myoblasts and multinucleated myotubes *in vitro* which are indistinguishable from normal

myoblasts (Choi et al., page 7988, abstract and materials and methods section, pages 7988-7989). Both Watt et al. and Choi et al. provide the motivation for further transforming fibroblasts which encode dystrophin with a second viral vector encoding myoD. Watt et al. teaches that transduced fibroblasts are preferred over patient myoblasts since patient myoblasts have already passed through several bouts of degeneration/regeneration, and donor fibroblasts can fuse in vivo to make a multinucleate cell which can behave like a muscle cell (Watt et al., page 3, lines 15-22). Choi et al. further provides motivation for transducing dermal fibroblasts with myoD by teachings that fibroblasts can be converted to myoblasts by expression of myoD. Thus, based on the motivation for transducing dermal fibroblasts that are capable of behaving like myoblasts with a therapeutic gene as taught by Watt et al., and the teachings of Choi et al. that transduction of dermal fibroblasts with the myoD gene results in the differentiation of the fibroblasts to actual myoblasts, it would have been *prima facie* obvious to the skilled artisan at the time of filing to co-express the myoD gene in the fibroblasts taught by Watt et al. in order to differentiate the dystrophin expressing fibroblasts into dystrophin expressing myoblasts. Further, based on the successful transduction of primary fibroblasts with viral vectors encoding dystrophin and myoD as taught by Watt et al. and Choi et al., the skilled artisan would have had a reasonable expectation of success in preparing a modified fibroblast which has been co-transduced with both the genes for dystrophin and myoD. Furthermore, Murry et al. supplements Choi et al. by teaching the use of an adenovirus encoding myoD to infect fibroblasts *in vitro* and *in vivo* resulting in myoconversion (Murry et al., pages 2211-2212). Murry et al. provides motivation for using the adenovirus encoding myoD over the retrovirus encoding myoD taught by Choi et al. by teaching that fibroblasts infected with adenovirus encoding myoD demonstrated up to 14%

myoconversion compared to 5% or less observed with the retrovirus taught by Choi et al. Thus, based on the increased level of myoconversion using adenovirus encoding myoD over retrovirus encoding myoD, as demonstrated by Murry et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to use an adenovirus encoding myoD to infect dermal fibroblasts as taught by Choi et al. Based on the successful use of the adenovirus encoding myoD to infect and myoconvert cardiac fibroblasts, the skilled artisan would have had a reasonable expectation of success in using the adenovirus encoding myoD to infect and myoconvert dermal fibroblasts.

Applicant's amendments to the claims have resulted in the following new grounds of rejection of the claims under 35 U.S.C. 103(a).

Claims 11, and 13-16 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/09373, 28 March 1996, hereafter referred to as Watt et al., in view of Choi et al. (1990), PNAS, Vol. 87, 7988-7992, and further in view of Murry et al. (1996) J. Clin. Invest., Vol. 98 (10), 2209-2217, and Salvatori et al. (1995) J. Cell. Science, Vol. 108, 2733-2739. The applicant claims methods for increasing the frequency of myogenic conversion of genetically modified dermal fibroblasts comprising ex-vivo transduction of dermal fibroblasts with a therapeutic gene, and transient transfection of the dermal fibroblasts with a vector encoding a muscle lineage commitment gene under control of a strong promoter, wherein the vector is an adenoviral vector, wherein the muscle lineage commitment gene is myoD, and wherein the rate of myogenic conversion is greater than 40%.

Watt et al. teaches the transduction of dermal fibroblasts which have been removed from a patient with a muscular disorder with a vector encoding dystrophin, a gene therapeutic for muscular dystrophy (Watts et al., page 6, and pages 23-24, claims 1-24). Watt et al. does not specifically teach the further modification of these cells with a viral vector encoding myoD. Choi et al. supplements Watt et al. by teaching that primary fibroblasts transduced with a retrovirus encoding myoD differentiate into striated mononucleated myoblasts and multinucleated myotubes *in vitro* which are indistinguishable from normal myoblasts (Choi et al., page 7988, abstract and materials and methods section, pages 7988-7989).

Both Watt et al. and Choi et al. provide the motivation for further transforming fibroblasts which encode dystrophin with a second viral vector encoding myoD. Watt et al. teaches that the preferable method of treatment of muscular dystrophy would modify the patient's own myoblasts to express dystrophin (Watt et al., pages 2-3, bridging paragraph). However, because the use of myoblasts from patients with muscular dystrophy for gene therapy of MD pose several problems because the disease myoblasts have already passed through several bouts of degeneration/regeneration, Watt proposes using transduced fibroblasts since donor fibroblasts can fuse in vivo to make a multinucleate cell which can behave like a muscle cell (Watt et al., page 3, lines 15-22). Choi et al. supplements Watt et al. by teaching that fibroblasts can be converted to myoblasts by expression of myoD. Thus, based on the motivation for utilizing cells that are capable of behaving like myoblasts for the therapy of MD taught by Watt et al., and the teachings of Choi et al. that transduction of dermal fibroblasts with the myoD gene results in the differentiation of the fibroblasts to actual myoblasts, it would have been *prima facie* obvious to the skilled artisan at the time of filing to co-express the myoD gene in the fibroblasts

taught by Watt et al. in order to differentiate the dystrophin expressing fibroblasts into dystrophin expressing myoblasts for use in the therapy of muscular dystrophy. Further, based on the successful transduction of primary fibroblasts with viral vectors encoding dystrophin and myoD as taught by Watt et al. and Choi et al., the skilled artisan would have had a reasonable expectation of success in preparing a modified fibroblast which has been co-transduced with both the genes for dystrophin and myoD.

The teachings of Watt et al. in view of Choi et al. differ from the instant invention in that Choi et al. does not teach the use of an adenovirus to express myoD in the dermal fibroblasts. Murry et al. supplements Choi et al. by teaching the use of an adenovirus encoding myoD to infect cardiac fibroblasts *in vitro* and *in vivo* resulting in myoconversion (Murry et al., pages 2211-2212). Murry et al. further provides motivation for using the adenovirus encoding myoD over the retrovirus encoding myoD taught by Choi et al. by teaching that fibroblasts infected with adenovirus encoding myoD demonstrated up to 14% myoconversion compared to 5% or less observed with the retrovirus taught by Choi et al. Thus, based on the increased level of myoconversion using adenovirus encoding myoD over retrovirus encoding myoD, as demonstrated by Murry et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to use an adenovirus encoding myoD to infect fibroblasts over the retrovirus taught by Choi et al.. Salvatori et al. further provides motivation for infecting dermal fibroblasts with adenovirus encoding myoD over cardiac fibroblasts in methods of myoconversion by teaching that dermal fibroblasts have a substantially greater capacity to myoconvert than cardiac fibroblasts (Salvatori et al., page 2736, column 1, paragraph 1, and Table I on page 2738). In Table I, Salvatori shows that dermal fibroblasts show 8X the rate of myoconversion as cardiac

fibroblasts. and to use those dermal fibroblasts in the methods of *ex vivo* gene therapy taught by Watt et al. Therefore, based on the increased level of myoconversion of fibroblasts achieved using adenovirus encoding MyoD over retrovirus encoding MyoD, and the naturally greater capacity of dermal fibroblasts to myoconvert as compared to cardiac fibroblasts, it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute the adenovirus encoding myoD for the retrovirus encoding myoD in the method of myoconversion of dermal fibroblasts taught by Choi et al. and Watt et al. Further, based on the successful use of the adenovirus encoding myoD to infect and myoconvert cardiac fibroblasts at a rate of 14% and the teachings of Salvatori et al that dermal fibroblasts are 8X better at myoconversion than cardiac myoblasts, the skilled artisan would have had a reasonable expectation of success in using the adenovirus encoding myoD to infect and myoconvert dermal fibroblasts at a rate of 40% or more.

Applicant's arguments as they apply to these new grounds of rejection have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons discussed in detail below.

The applicant has argued that the methods taught by Watt et al. result in the spontaneous conversion of the transfected dermal fibroblasts to muscle cells in vivo, and that the rate of spontaneous conversion is too low to make this methodology practical for treating muscle disorders in a patient. In contrast, the applicant states that their methods result in a higher frequency of myogenic conversion than that observed by Watt et al. In response, please note that the applicant claims do not recite the treatment of muscle disorders. The instant methods are directed to methods of increasing the frequency of myogenic conversion of transduced dermal

fibroblasts *ex vivo*. As such, the potential of cells produced by this *ex vivo* method for successfully treating disease in patients is not relevant to the patentability of these claims under 103(a). Watt et al. provides motivation for transducing dermal fibroblasts capable of myoconversion with a therapeutic gene *ex vivo*. In view of the claims as written, it is not required that Watt et al. provide any expectation of success for therapeutic methods using these transduced dermal fibroblasts since methods of therapy are not claimed.

The applicant further argues that Choi et al. does not supplement Watt et al. because Choi et al. teaches the use of an integrating retroviral vector and that the rate of myogenic conversion using this vector is low. The office does not refute that the rate of myoconversion of the transduced dermal fibroblasts taught by Choi et al. is low. However, Choi et al. has been cited for providing motivation for expressing myoD in dermal fibroblasts to stimulate myoconversion *in vitro*. This is important since Watt et al. teaches that spontaneous myoconversion occurs *in vivo*. Thus, despite the low rate of myoconversion using retroviral myoD, the skilled artisan would have been motivated to transduce the dermal fibroblasts encoding dystrophin with myoD *in vitro* in order to produce myoblasts encoding dystrophin. Watt et al. already provides motivation for making autologous normal myoblasts encoding dystrophin.

Regarding Murry et al., the applicant argues that Murry et al. teaches the myoconversion of cardiac fibroblasts transduced with an adenovirus encoding myoD and not dermal fibroblasts. The applicant further argues that Murry only teaches a 14% rate of myoconversion and that the skilled artisan would not have reasonably predicted success in achieving 40% or greater myoconversion by transducing dermal fibroblasts with myoD. In response, the previous grounds of rejection has been modified to include the teachings of Salvatori et al. Salvatori et al. teaches

that dermal fibroblasts have 8X the capacity to myoconvert than cardiac fibroblasts. Since cardiac fibroblasts encoding myoD myoconverted as a rate of 14% versus a spontaneous rate of 0.7% as taught by Salvatori et al., and dermal fibroblasts have a much greater spontaneous conversion rate, the skilled artisan would reasonably have expected that the rate of myoconversion of dermal fibroblasts transduced with adenovirus encoding myoD would be substantially greater than 14%. Therefore, based on the substantially greater capacity of dermal fibroblasts to myoconvert over cardiac fibroblasts, the skilled artisan would have had a reasonable expectation of success in generating 40% myoconversion of dermal fibroblasts transduced with the adenovirus encoding myoD taught by Murry et al. As noted in previous office actions, obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

Regarding applicant's comments that the instant methods resulted in unexpected beneficial results, please note that the MPEP states that the arguments of counsel cannot take the place of evidence in the record . *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716,718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results. MPEP 716.01(c). Furthermore, the rejection of record now relies on Salvatori et al. which provides sufficient expectation of success in generating rates of myoconversion of dermal fibroblasts transduced with adenovirus encoding myoD substantially greater than 14%. Thus, for the reasons discussed in detail above, applicant's arguments do not overcome the rejection of the claims as written.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Please note that the United States Patent and Trademark Office will begin to move to the new campus in Alexandria, Virginia, in December 2003. The examiners of Art Unit

1632 will be moving in January 2004. As of January 13, 2004, this examiner's phone number will be (571) 272-0737, and that of the examiner's supervisor will be (571) 272-0734.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER